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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/648,183	08/25/00	BOTSTEIN D	P2533C1

HM22/1222

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EXAMINER	
SORBELLO,E	
ART UNIT	**PAPER NUMBER**
1633	4

DATE MAILED: 12/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/648,183	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

file copy

DETAILED ACTION

Response to Amendment

1. Preliminary amendment filed 10/14/00 as paper No. 3A is acknowledged. Receipt of corrected oath/declaration indicating applications from which instant application claims benefit, is acknowledged.

Priority

2. If applicant desires priority under 35 U.S.C.119 (e) or 120, based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. A statement reading "This is a continuation of Application No. 09/234,730, filed 01/21/1999." should be entered following the title of the invention or as the first sentence of the specification.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 27, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the phrase "pathological condition is".

The claim is incomplete as it does not refer to any pathological condition.

Claims 29 and 30 depend from 27 and are therefore rejected.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

5. Claims 24-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a non-human animal comprising homologously recombined DNA wherein the CT-1 gene of the animal is altered such that the CT-1 polypeptide of the animal is defective or absent. The claims are further directed to the aforementioned animal wherein the CT-1 gene is absent wherein the pathological condition is cardiac hypertrophy, wherein the animal is a rodent, mouse or rat.

The specification fails to teach the generation of any transgenic animal, with the aforementioned defective CT-1 gene or wherein the CT-1 gene is completely absent and wherein the CT-1 polypeptide of the animal is defective or absent, except by prophetic consideration. The specification states that the generation of a transgenic animal or knockout animal can be characterized for instance by their ability to defend against a pathological condition and by their development of a pathological condition due to the absence of the CT-1 polypeptide.

The art of transgenics and generating transgenic animals is not a predictable art with respect to transgene behavior or resultant phenotype. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species. For example, Mullins *et al.* teaches (page S37) that since exogenous DNA integrates randomly into chromosomes, position effect can have a major influence on expression of transgenes and that "in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." Mullins, *et al.* further teaches (see abstract) that the with regard to ES cell technology, germline transmission has only been achieved with mouse ES cells. The lack of any evidence for use of ES cell technology to generate transgenic animals other than the mouse supports the unpredictability of using said technology to generate similar effect/phenotype from one species to another. Considerations must be given to different function of different DNA constructs in different species of organisms, with regard to promoter effects, enhancer effects, coding and non-coding sequences in the transgene construct, sites of integration of the transgene, and methods of construct delivery. The specification does not enable one skilled in the art of transgenics to make any transgenic non-human animal.

Bradley, *et al.* teaches that with regard to ES cells, it has not been demonstrated that they can proliferate and differentiate in an embryo *in vivo*. The specification (see page 26 lines 17-26) cites references Bradley et al , Li et al., wherein selected cells are injected into a blastocyst of an animal such as a mouse or rat to form

aggregate chimeras. The specification also stated that these references taught that a chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. It is not clear from the specification that an actual knock-out mouse or rat which lacked the CT-1 gene and thus was defective in the CT-1 polypeptide was actually generated. As such it is unpredictable that the knock out mouse or rat would be able to be generated. The use of "knockout" mice is unpredictable because the use of the mouse is dependent upon whether the phenotype that is required or desired is conferred. Genes which have important *in vitro* functions often are redundant *in vivo* and therefore does not result in the desired phenotype (see Fassler et al, page 324, ¶2). In order to use the knockout mice the expression of the particular gene must be completely depleted or reduced enough such that the function that the skilled practician is studying, is affected. Often the expression of particular genes can be reduced quite drastically, but still have no effect overall. Further, it is unpredictable as to whether or not the CT-1 gene would be fully knocked out in another species and that the phenotype of the pathological condition of cardiac hypertrophy would or would not be present. Additionally it is not clear that all animals have the CT-1 gene and that if present it is expressed in all of its cells. The nucleotide sequence of all CT-1 genes for all species of animals is not known, and therefore it is not clear that homologous recombination will take place, in all animals.

The state of the art at the time of filing was such that a number of significant limitations regarding the production of transgenic animals exist.

Further, the specification lacks any examples of transgenic or knock out animals wherein the CT-1 polypeptide is defective and evidence that heterozygotic mice were generated. Heterozygotes can vary with regard to phenotype since it is unpredictable as to what level of protein will be produced due to the removal of one allele of the gene. Gene inactivation mechanisms (e.g. CpG methylation) may result in inactivation of the one allele in one animal and/or species and not in another. One of skill in the art would not be able to predict the phenotype of a heterozygotic CT-1 defective mouse and/or animal.

In view of such, it would require undue experimentation to determine whether or not the same phenotype would be expressed in any transgenic animal in view of the lack of working examples, lack of guidance, unpredictability in the art and breadth of the claims. The amount of experimentation would entail the generation of a representative set of animals from different species to illustrate that transgene expression results in reproducible display of the disclosed phenotype in all animals. Further, heterozygotes would have to be generated in multiple species and in multiple animals and concomitant phenotype would have to be predicted. In view of such, the invention is not enabled.

Conclusion

6. Claims 24-30 are rejected.

7. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark

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